

REMARKS

This Paper is being filed in response to the Office Action dated August 30, 2004. The claims under consideration are claims 1-12, 21-25, 31-37 and 39-43.

Independent claims 1, 22 and 39 have been amended to incorporate the feature that the uricase is comprises 12-30 strands of PEG per uricase protein unit. Support for the amendment may be found at page 9, lines 28-29 where it is taught that some embodiments of uricase have the amino acid sequence set forth in the sequence listing. Further at page 16, lines 30-32 through page 17, line 1, it is taught that isolated uricase had an apparent molecular weight by SDS-PAGE of 34 kDa, and at page 22 wherein it is taught that the trinitrobenzenesulfonic acid assay was used to determine the average number of PEG molecules covalently attached to primary amines in "each uricase protein." Finally, page 12, lines 14-30 clearly shows that a unit of *Candida* uricase, for example has 32 lysine residues to which PEG molecules may be attached and states that 1 to 32 PEG molecules can be attached to the protein, preferably between 5 and 30 (or about 15% to about 95%). Therefore, it is clear that when the specification refers to the number of PEG molecules attached to the protein, it is referring to each 34 kDa uricase protein unit. Dependent claims 10-12, 21, 24, 25, and 41-43 have been amended to recite "uricase protein unit" for consistency.

Claims 1, 22 and 39 have been further amended to recite that the number of PEG molecules attached to uricase is between 12 and 30. Support for the amendment may be found, for example in the specification at page 12, lines 21-24. While there is no *in haec verba* support for 12 molecules of PEG per uricase protein, Applicants respectfully invite the Examiner's attention to the MPEP 2163.06 III where range limitations are discussed. In that discussion, the MPEP notes that in *In re Wertheim*, the range disclosed in the original specification included a range of "25%-60%" and specific examples of "36%" and "50%." A new claim limitation of "at least 35%" did not meet the Written Description Requirement as there was no upper limit (*i.e.*, it was outside the original 25%-60% upper range limit), however a limitation of "between 35% and 60%" did meet the written description requirement (note that 35% was not a specific example, but merely fell within the range of the original disclosure). This case is very similar to the situation of the present claims. It

would be immediately apparent to those of skill in the art that the inventor had possession of this range at the time of filing. As noted in MPEP 2163.06 III, the Federal Circuit stated in *Union Oil of Cal. V. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 U.S.P.Q.2d 1227, 1232-33 (Fed. Cir. 2000) “[T]he Patent Act and this court’s case law require only *sufficient* description to show one of skill in the ...art that the inventor possessed the claimed invention at the time of filing.” (emphasis added). Thus, Applicants respectfully submit that there is sufficient support for 12 molecules of uricase per protein unit in the specification as filed. No new matter is added.

The Office Action rejects claims 1-12, 21-25, 31-37 and 39-43 under 35 U.S.C. §112, first paragraph as allegedly not enabled by the Specification. The Office Action alleges that one of skill in the art, reading the actual data along with the general recitations of the specification “would believe applicants’ data shown in Table 1 but would not believe these other speculative results in the specification.” Applicants respectfully disagree. First of all the person of ordinary skill in the art would be well aware that the covalent attachment of polyethylene glycol to proteins was well established.

Applicants respectfully traverse the rejection because Applicants have demonstrated that uricase covalently bound to polyethylene glycol of weight average molecular weights of 12,000 to 40,000 retains approximately 75% of the biological activity of native uricase, and as the molecular weight of the polyethylene glycol bound to uricase increases from 5,000 to 30,000, the circulating half-life of the PEG-uricase increases from 8 to 84 hours.

Previously submitted
As explained in the attached Declaration of Mike A. Clark, an inventor of the subject matter defined by the claims of the present application, Applicants have performed experiments in which purified *Candida utilis* uricase was covalently bound to polyethylene glycol of weight average molecular weights of 5,000; 12,000; 20,000; 30,000; or 40,000 via a succinimidyl succinate linking group. The PEG-uricase conjugates retained a substantial amount of enzymatic activity. More specifically, uricase-PEG 5,000; uricase-PEG 12,000; uricase-PEG 20,000; uricase-PEG 30,000; and uricase PEG 40,000 retained 55%, 73%, 75%, 74%, and 76% of the enzymatic activity of native uricase, respectively. In addition, as the molecular weight of the polyethylene glycol to which the uricase was bound increased, the circulating half-life of the pegylated uricase also increased. For example, uricase-PEG 5,000; uricase-PEG 12,000; uricase-PEG 20,000; uricase-PEG 30,000; and uricase PEG 40,000 had

circulating half-lives of 8, 24, 72, 84, and 77 hours, respectively. Applicants have therefore demonstrated that purified *Candida utilis* uricase covalently bound to polyethylene glycol of weight average molecular weights of 12,000 to 40,000 retained approximately 75% of the biological activity of native uricase, and as the molecular weight of the polyethylene glycol bound to uricase increased from 5,000 to 30,000, the circulating half-life of the PEG-uricase increased from 8 to 84 hours.

Applicants, accordingly, respectfully request withdrawal of the rejection.

The Office Action rejects claims 1-12, 21-25, 31-37 and 39-43 under 35 U.S.C. §103(a), as allegedly obvious over U.S. Patent No. 6,576,235 to Williams *et al.* ("WILLIAMS"). Applicants have amended claims 1, 22 and 39 to include the features that the uricase comprises 12-30 strands of PEG per uricase protein. Williams specifically teaches uricase in which high molecular weight PEG molecules were present in an amount of about 2 to 10 stands per subunit with widely varying results depending on the source of uricase (see Col. 7, lines 55-60; Col. 10, lines 66-67 through Col. 11, lines 1-9). It would not have been obvious to one of skill in the art to use a uricase protein unit coupled to 12 to 30 strands of PEG having a molecular weight between 12,000 to 30,000 with a reasonable expectation of success as WILLIAMS teaches tetrameric uricase having only between 2 and 10 strands of PEG per subunit and WILLIAMS does not teach or suggest that a greater number of strands would be expected to work better. The reasoning that more stands of PEG would work better is not supported by the data in Williams and is simply relying on an "obvious-to-try" standard which is an improper standard for an obviousness rejection. Applicants demonstrate that a higher number of PEG molecules per protein subunit are effective.

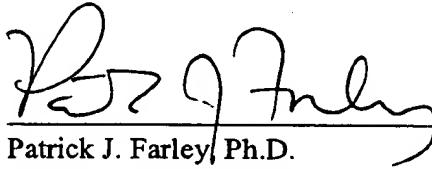
Withdrawal of the rejection is respectfully requested.

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Applicants earnestly submit that the claims are in condition for allowance and respectfully request prompt allowance of the claims as amended.

Respectfully submitted,



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